

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
7 June 2001 (07.06.2001)

PCT

(10) International Publication Number  
**WO 01/39745 A2**

- (51) International Patent Classification: **A61K 9/14**, 9/12, 31/165
- (21) International Application Number: **PCT/EP00/11894**
- (22) International Filing Date:  
28 November 2000 (28.11.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
9928311.1 30 November 1999 (30.11.1999) **GB**
- (71) Applicant (for all designated States except AT, US): **NOVARTIS AG [CH/CH]**; Schwarzwaldallee 215, CH-4058 Basel (CH).
- (71) Applicant (for AT only): **NOVARTIS-ERFINDUNGEN [AT/AT]**; Verwaltungsgesellschaft m.b.H., Brunnner Strasse 59, A-1230 Vienna (AT).
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): **HAEBERLIN, Barbara [CH/CH]**; Haselrain 77, CH-4125 Riehen (CH).
- (74) Agent: **BECKER, Konrad**; Novartis AG, Corporate Intellectual Property, Patent & Trademark Department, CH-4002 Basel (CH).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:  
— Without international search report and to be republished upon receipt of that report.
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



**WO 01/39745 A2**

(54) Title: **USE OF ORGANIC COMPOUNDS IN THE TREATMENT OF DISEASE**

(57) Abstract: The use of a dry powder comprising (A) formoterol, or a pharmaceutically acceptable salt or solvate thereof, or solvate of said salt, and (B) a pharmaceutically acceptable particulate diluent or carrier in an amount of from 400 µg to 5000 µg per µg of (A) for the preparation of an inhalable medicament for the treatment of chronic obstructive pulmonary disease.

Use of organic compounds in the treatment of disease

This invention relates to the use of organic compounds in the treatment of chronic obstructive pulmonary disease (COPD), both reversible and irreversible COPD, reversibility being defined by reference to the effect of inhalation of a standard dose of a short-acting beta-2 agonist bronchodilator such as salbutamol on the forced expiratory volume in 1 second (FEV<sub>1</sub>) measured by spirometry. The characteristics of different stages of COPD are described in the Official Statement of the American Thoracic Society (ATS): Am J Respir Crit Care Med Vol 152, pp 577-120, 1995, and a Consensus Statement of the European Respiratory society (ERS): European Respiratory Journal 1995,8,1398-1420.

It has now surprisingly been found, in accordance with the invention, that formoterol or a pharmaceutically acceptable salt or solvate thereof or solvate of said salt, each hereinafter alternatively referred to as the formoterol active ingredient, is particularly effective in the treatment of COPD when administered by inhalation as a dry powder in admixture with a diluent or carrier in an amount of from 400µg to 5,000 µg per µg of formoterol active ingredient. Administration of such a mixture by inhalation to COPD patients facilitates significant sustained bronchodilation, a very good safety profile, important e.g. for the treatment of COPD without significant concomitant cardiovascular effects, and significant improvement in Quality of Life as assessed by the St George's Respiratory Questionnaire (SGRQ).

Accordingly, the present invention provides, in one aspect, the use of a dry powder comprising (A) formoterol, or a pharmaceutically acceptable salt or solvate thereof, or solvate of said salt, and (B) a pharmaceutically acceptable particulate diluent or carrier in an amount of from 400 µg to 5,000 µg per µg of (A) in the preparation of an inhalable medicament for the treatment of chronic obstructive pulmonary disease.

In a related aspect, the present invention provides a pharmaceutical composition in the form of a dry powder comprising (A) and (B) as hereinbefore defined for use in the treatment of chronic obstructive pulmonary disease.

In another aspect, the present invention provides a method of treating chronic obstructive pulmonary disease which comprises administering by inhalation to a subject in need of such

treatment an effective amount of a dry powder comprising (A) formoterol, said formoterol being in free form or in the form of a pharmaceutically acceptable salt or solvate thereof or in the form of a solvate of such a salt, and (B) a pharmaceutically acceptable particulate diluent or carrier in an amount of from 400  $\mu\text{g}$  to 5,000  $\mu\text{g}$  per  $\mu\text{g}$  of (A).

In a further aspect, the present invention provides the use of a dry powder comprising (A) formoterol, or a pharmaceutically acceptable salt or solvate thereof, or solvate of said salt, and (B) a pharmaceutically acceptable particulate diluent or carrier in an amount of from 400  $\mu\text{g}$  to 5,000  $\mu\text{g}$  per  $\mu\text{g}$  of (A), said dry powder being substantially free from fluticasone propionate, mometasone furoate or tiotropium salts, for the preparation of an inhalable medicament for the treatment of chronic obstructive pulmonary disease.

The formoterol active ingredient (A) may be in any isomeric form or mixture of isomeric forms, for example a pure enantiomer, particularly the R,R-enantiomer, a mixture of enantiomers, a racemate or a mixture thereof. Pharmaceutically acceptable salts of formoterol include acid addition salts with inorganic acids such as hydrochloric acid, hydrobromic acid, sulphuric acid or phosphoric acid, or organic acids such as acetic, succinic, glutaric, maleic, fumaric, citric, tartaric, lactic, benzoic, salicylic, p-hydroxybenzoic, p-methoxybenzoic, hydroxynaphthoic, methanesulfonic, benzenesulfonic, or p-toluenesulfonic acid. Suitable solvates of formoterol and pharmaceutically acceptable salts thereof include hydrates. A preferred form of formoterol for use in accordance with the invention is formoterol fumarate, especially formoterol fumarate dihydrate, conveniently in racemic form. Formoterol, salts and hydrates thereof and salt hydrates thereof as hereinbefore described may be prepared by known methods, for example as described in US3994974 or US5684199.

Accordingly, in a preferred embodiment, the present invention provides the use of a dry powder consisting, or consisting essentially, of (A) formoterol fumarate dihydrate and (B) a pharmaceutically acceptable diluent or carrier in an amount of from 400  $\mu\text{g}$  to 5,000  $\mu\text{g}$  per  $\mu\text{g}$  of (A) for the preparation of an inhalable medicament for the treatment of chronic obstructive pulmonary disease.

Suitable diluents or carriers include saccharides and/or sugar alcohols, e.g. monosaccharides, disaccharides and polysaccharides such as glucose, arabinose, dextrose, fructose, ribose, mannose, sucrose, trehalose, lactose, maltose or dextran, sugar alcohols such as mannitol

and mixtures of two or more thereof. A preferred diluent or carrier is lactose, particularly in the form of the monohydrate. The diluent or carrier is generally present in an amount of 400 to 4000  $\mu\text{g}$ , for example 800 to 3000  $\mu\text{g}$ , more preferably 1000 to 2500  $\mu\text{g}$ , especially 2000 to 2500  $\mu\text{g}$ , per  $\mu\text{g}$  of formoterol active ingredient (A). The mean particle diameter of the formoterol active ingredient (A) is preferably up to 10  $\mu\text{m}$ , more preferably up to 5  $\mu\text{m}$ , especially 1 to 5  $\mu\text{m}$ . The diluent or carrier (B) may be present in the dry powder in the form of particles having, for example, a maximum diameter of 300  $\mu\text{m}$ , a preferred maximum being 212  $\mu\text{m}$ . The diluent or carrier (B) may conveniently have a median particle diameter of 40 to 100  $\mu\text{m}$ , e.g. 50 to 75  $\mu\text{m}$ . The particle size of the formoterol active ingredient (A), and that of the diluent or carrier (B), can be reduced to the desired level by conventional methods, for example by grinding in an air-jet mill, ball mill or vibrator mill, by sieving, by microprecipitation, by spray-drying, by lyophilisation or by recrystallisation from supercritical media.

In a preferred embodiment of the invention, the dry powder is in a capsule, usually of a pharmaceutically acceptable natural or synthetic polymer such as gelatin or hydroxypropyl methylcellulose, the capsule containing a unit dose of formoterol active ingredient (A). Doses of formoterol active ingredient (A) to be inhaled in accordance with the invention may be, in general, from 1  $\mu\text{g}$  to 60  $\mu\text{g}$ . When (A) is formoterol fumarate dihydrate, the dose may be, for example, from 6  $\mu\text{g}$  to 48  $\mu\text{g}$ . Preferred doses are from 6  $\mu\text{g}$  to 36  $\mu\text{g}$ , for example 6  $\mu\text{g}$ , 12  $\mu\text{g}$ , 18  $\mu\text{g}$ , 24  $\mu\text{g}$ , 30  $\mu\text{g}$ , or 36  $\mu\text{g}$ , the 12  $\mu\text{g}$  and 24  $\mu\text{g}$  being especially preferred and the 12  $\mu\text{g}$  dose the most preferred. These doses may be administered once or twice daily, preferably twice daily, the preferred maximum daily dose being 48  $\mu\text{g}$ . For on demand usage, the 6  $\mu\text{g}$  or 12  $\mu\text{g}$  dose is preferred, being inhaled as needed in accordance with a preferred maximum daily dose of 48  $\mu\text{g}$ . When the dry powder is in a capsule containing a unit dose of (A), e.g. 6  $\mu\text{g}$ , 12  $\mu\text{g}$  or 24  $\mu\text{g}$  of (A), the amount of diluent/carrier is preferably such as to bring the total weight of dry powder per capsule to between 5 mg and 25 mg, e.g. to 5 mg, 10 mg, 15 mg, 20 mg or, especially, 25 mg.

In especially preferred embodiments the dry powder is in a capsule, the capsule containing 12  $\mu\text{g}$  of formoterol active ingredient (A) and 4988  $\mu\text{g}$  to 49988  $\mu\text{g}$ , for example 4988  $\mu\text{g}$  or 9988  $\mu\text{g}$  or 14988  $\mu\text{g}$ , more preferably 19988  $\mu\text{g}$  to 24988  $\mu\text{g}$ , for example 19988  $\mu\text{g}$  or, especially, 24988  $\mu\text{g}$  of diluent or carrier (B).

As will be understood by those skilled in the art, a dry powder contained in a capsule may be inhaled by inserting the capsule in a dry powder inhalation device adapted to pierce a capsule containing the dry powder on actuating the device, thereby releasing the dry powder for inhalation by the user - a dry powder capsule inhaler. Such devices are well known in the art and are commercially available. For example, a suitable inhalation device is described in US3991761, which is incorporated herein by reference, particularly as described in the claims of US3991761 and as described with reference to the drawings of US3991761; this device may be modified by coating the capsule-piercing pins with a polymer, as described in WO99/45987. A preferred inhalation device is one adapted to receive a single capsule containing the dry powder, i.e. a single capsule inhaler, for example the commercially available Aerolizer® inhaler.

In another preferred embodiment of the invention, the dry powder may be in a reservoir of a multi-dose dry powder inhaler adapted to deliver a unit dose, for example 5 µg, 6 µg, 9 µg, 10 µg, 12 µg, 15 µg, 18 µg, 20 µg, 24 µg, 25 µg, 30 µg or 36 µg, preferably from 5 to 15 µg of formoterol active ingredient (A), particularly formoterol fumarate dihydrate, per actuation, for example from a powder having a formoterol fumarate dihydrate:lactose weight ratio of 5:4995, 5:9995, 5:14995, 10:4990, 10:9990, 10:14990, 12:4988, 12:9988, 12:14998, 15:9985 or 15:14985. Multi-dose dry powder inhalers are well known in the art and are commercially available. For example, a suitable multi-dose inhaler is that described in WO97/20589.

Treatment of COPD in accordance with the invention includes treatment of reversible or irreversible, mild, moderate or severe COPD (including chronic bronchitis and emphysema) and conditions associated therewith, e.g. bronchospasm, loss of lung function, loss of exercise capacity, breathlessness, dyspnea or loss of lung elasticity. Thus treatment of COPD in accordance with the invention includes maintenance (prophylactic) treatment or on-demand or rescue treatment of bronchospasm associated with COPD, treatment to slow progressive loss of lung function, treatment to improve exercise capacity, and treatment to improve Quality to Life according to the SGRQ.

The effect of compositions of the invention in the treatment of COPD can be monitored in a conventional manner, e.g. by determining parameters such as forced expiratory volume in 1 second (FEV<sub>1</sub>), vital capacity (VC), forced vital capacity (FVC), Quality of Life, peak expiratory flow (PEF), exercise capacity (e.g. Shuttle Walking Test) and lung compliance

(CL) at intervals during treatment. Quality of Life may be measured according to the SGRQ (P.W. Jones et al, Respir Med. 1991; 85 (Suppl B): 25-31).

The invention is illustrated by the following Examples.

Example 1

Gelatin capsules suitable for use in a capsule inhaler are prepared, each capsule containing a dry powder consisting of 6 µg of formoterol fumarate dihydrate which has been ground to a mean particle diameter of 1 -5 µm in an air jet mill and 4994 µg of lactose monohydrate having a particle diameter of below 212 µm. These capsules are used in the treatment of COPD patients by inserting a capsule into the capsule chamber of the inhaler described in US3991761 and actuating the piercing devices to perforate the capsule and release the dry powder when air is inhaled through the capsule chamber by a patient.

Examples 2 - 29

Example 1 is repeated but using the amounts of the formoterol fumarate dihydrate and the lactose monohydrate shown in the table below in place of the amounts used in that Example:

Example	Formoterol Fumarate Dihydrate (µg)	Lactose Monohydrate (µg)
2	6	9994
3	6	14994
4	6	19994
5	6	24994
6	12	4988
7	12	9988
8	12	14988
9	12	19988
10	12	24988
11	12	29988
12	18	9982

13	18	14982
14	18	19982
15	18	24982
16	18	29982
17	24	9976
18	24	14976
19	24	19976
20	24	24976
21	24	29976
22	30	14970
23	30	19970
24	30	24970
25	30	29970
26	36	14964
27	36	19964
28	36	24964
29	36	29964

**Example 30**

Two groups of patients suffering from COPD are treated with formoterol. One group has reversible COPD, showing at least 15% increase in FEV<sub>1</sub> 30 minutes after inhaling 200 µg of salbutamol. The other group has irreversible COPD, showing less than 15% increase in FEV<sub>1</sub> 30 minutes after inhaling 200 µg of salbutamol. Both groups are treated by inhalation twice daily for 12 weeks from a capsule containing a dry powder consisting of 12 µg of formoterol fumarate dihydrate having a mean particle diameter of 1 to 5 µm and 24988 µg of lactose monohydrate having a particle diameter below 212 µm, using an Aerolizer® inhaler. After treatment for 12 weeks, the patients' lung function (FEV<sub>1</sub>) is measured at intervals for 12 hours after dosing, the measured FEV<sub>1</sub> is plotted against time after dosing and the area under the curve (AUC) of the resulting plot is determined.

Claims

1. The use of a dry powder comprising (A) formoterol, or a pharmaceutically acceptable salt or solvate thereof, or solvate of said salt, and (B) a pharmaceutically acceptable particulate diluent or carrier in an amount of from 400  $\mu\text{g}$  to 5000  $\mu\text{g}$  per  $\mu\text{g}$  of (A) for the preparation of an inhalable medicament for the treatment of chronic obstructive pulmonary disease.
2. The use of a dry powder comprising (A) formoterol, or a pharmaceutically acceptable salt or solvate thereof, or solvate of said salt, and (B) a pharmaceutically acceptable particulate diluent or carrier in an amount of 400  $\mu\text{g}$  to 5,000  $\mu\text{g}$  per  $\mu\text{g}$  of (A), said dry powder being substantially free from fluticasone propionate, mometasone furoate or tiotropium salts, for the preparation of an inhalable medicament for the treatment of chronic obstructive pulmonary disease.
3. Use according to claim 1 or 2, in which the formoterol (A) is in the form of formoterol fumarate dihydrate.
4. The use of a dry powder consisting, or consisting essentially, of (A) formoterol fumarate dihydrate and (B) a pharmaceutically acceptable diluent or carrier in an amount from 400  $\mu\text{g}$  to 5,000  $\mu\text{g}$  per  $\mu\text{g}$  of (A) for the preparation of an inhalable medicament for the treatment of chronic obstructive pulmonary disease.
5. Use according to any one of the preceding claims, in which the diluent or carrier (B) is a saccharide and/or sugar alcohol.
6. Use according to claim 5, in which the diluent or carrier (B) is lactose.
7. Use according to any one of the preceding claims, in which the diluent or carrier (B) is present in an amount of 800 to 3000  $\mu\text{g}$  per  $\mu\text{g}$  of (A).
8. Use according to any one of the preceding claims, in which the mean particle diameter of (A) is up to 10  $\mu\text{m}$ .
9. Use according to any one of the preceding claims, in which the dry powder is in a capsule, the capsule containing a unit dose of (A).



10. Use according to claim 9, in which the capsule contains 12  $\mu\text{g}$  of (A) and 19988 - 24988  $\mu\text{g}$  of diluent or carrier (B).

11. Use according to any one of claims 1 to 8, in which the dry powder is in a reservoir of a multi-dose dry powder inhaler adapted to deliver a unit dose of (A) per actuation.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
7 June 2001 (07.06.2001)

PCT

(10) International Publication Number  
**WO 01/39745 A3**

- (51) International Patent Classification<sup>7</sup>: A61K 9/14, 9/12, 31/165
- (21) International Application Number: PCT/EP00/11894
- (22) International Filing Date:  
28 November 2000 (28.11.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
9928311.1 30 November 1999 (30.11.1999) GB
- (71) Applicant (for all designated States except AT, US): NO-VARTIS AG [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).
- (71) Applicant (for AT only): NOVARTIS-ERFINDUNGEN [AT/AT]; Verwaltungsgesellschaft m.b.H., Brunner Strasse 59, A-1230 Vienna (AT).
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): HAEBERLIN, Barbara [CH/CH]; Haselrain 77, CH-4125 Riehen (CH).
- (74) Agent: BECKER, Konrad; Novartis AG, Corporate Intellectual Property, Patent & Trademark Department, CH-4002 Basel (CH).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:  
— with international search report
- (88) Date of publication of the international search report:  
20 December 2001
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 01/39745 A3

(54) Title: AEROSOL COMPOSITION COMPRISING FORMOTEROL

(57) Abstract: The use of a dry powder comprising (A) formoterol, or a pharmaceutically acceptable salt or solvate thereof, or solvate of said salt, and (B) a pharmaceutically acceptable particulate diluent or carrier in an amount of from 400 µg to 5000 µg per µg of (A) for the preparation of an inhalable medicament for the treatment of chronic obstructive pulmonary disease.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 00/11894

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 A61K9/14 A61K9/12 A61K31/165

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MAESEN F P V ET AL: "FORMOTEROL AS DRY POWDER INHALATION" CHEST, PARK RIDGE; IL, US, vol. 101, no. 5, 1992, pages 1376-1381, XP000911155 the whole document	1,2,5-11
X	WO 99 15182 A (TROFAST JAN ;ASTRA AB (SE); BAUER CARL AXEL (SE)) 1 April 1999 (1999-04-01) page 5, line 9 - line 19	1-3,5-11
X	WO 93 11773 A (ASTRA AB) 24 June 1993 (1993-06-24) page 9; example 3	1-3,5-11
	--- -/-- ---	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*G\* document member of the same patent family

Date of the actual completion of the international search

20 August 2001

Date of mailing of the international search report

28/08/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl  
Fax: (+31-70) 340-3016

Authorized officer

Boulois, D

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 00/11894

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 31351 A (TROFAST JAN ;ASTRA AB (SE)) 23 July 1998 (1998-07-23) page 2, line 20 - line 28	1
P,X	WO 00 47200 A (NOVARTIS ERFIND VERWALT GMBH ;NOVARTIS AG (CH); CLARKE JEREMY GUY) 17 August 2000 (2000-08-17) page 9; examples 2,3	1-3,5-11
A	BARNES P J: "Chronic obstructive pulmonary disease: new opportunities for drug development" TRENDS IN PHARMACOLOGICAL SCIENCES, ELSEVIER TRENDS JOURNAL, CAMBRIDGE, GB, vol. 19, no. 10, October 1998 (1998-10), pages 415-423, XP004156947 ISSN: 0165-6147 page 416	1
A	MAESEN B L P ET AL: "Effects of formoterol in apparently poorly reversible chronic obstructive pulmonary disease." EUROPEAN RESPIRATORY JOURNAL, vol. 13, no. 5, May 1999 (1999-05), pages 1103-1108, XP001020413 ISSN: 0903-1936 the whole document	1-11

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/11894

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9915182 A	01-04-1999	AU 9192898 A	12-04-1999
		BR 9812325 A	05-09-2000
		CN 1271287 T	25-10-2000
		EE 200000145 A	15-02-2001
		EP 1014993 A	05-07-2000
		NO 20001401 A	17-03-2000
		PL 339295 A	04-12-2000
		TR 200000726 T	21-09-2000
		ZA 9808516 A	19-03-1999
WO 9311773 A	24-06-1993	AU 673660 B	21-11-1996
		AU 3085892 A	19-07-1993
		CA 2123909 A	24-06-1993
		CZ 9401434 A	15-12-1994
		EP 1101493 A	23-05-2001
		EP 1086697 A	28-03-2001
		EP 0613371 A	07-09-1994
		HR 921445 A	31-12-1994
		HU 75156 A	28-04-1997
		JP 7502036 T	02-03-1995
		NO 942116 A	07-06-1994
		NZ 246050 A	21-12-1995
		SG 48301 A	17-04-1998
		SI 9200403 A	30-06-1993
		SK 73394 A	08-03-1995
		US 5674860 A	07-10-1997
		US 5972919 A	26-10-1999
WO 9831351 A	23-07-1998	AU 728835 B	18-01-2001
		AU 5785898 A	07-08-1998
		BE 1011401 A	03-08-1999
		BR 9806895 A	16-05-2000
		CZ 9902556 A	13-10-1999
		EE 9900294 A	15-02-2000
		EP 1009394 A	21-06-2000
		ES 2149082 A	16-10-2000
		FR 2759907 A	28-08-1998
		GR 98100022 A	30-09-1998
		HU 0000843 A	28-09-2000
		IE 980025 A	07-10-1998
		NL 1008021 C	07-10-1998
		NL 1008021 A	22-07-1998
		NO 993538 A	17-09-1999
		PL 334528 A	28-02-2000
		SK 95899 A	18-01-2000
		TR 9901692 T	21-09-1999
		US 5983956 A	16-11-1999
		US 6199607 B	13-03-2001
WO 0047200 A	17-08-2000	AU 2441900 A	29-08-2000